Remarks

Status Summary

Claims 16 and 23-38 are pending. Claims 16 and 23-38 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 16 and 23-36 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 16 and 23-32, 33, and 36-38 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Davis et al in view of Ozzello et al.. Claims 25 and 32 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Davis et al in view of Ozzello et al. in further view of Shan et al.. Claims 25 and 34 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Davis et al in view of Ozzello et al. in further view of Vose et al.. Claims 25 and 35 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Davis et al in view of Ozzello et al. in further view of Vose et al..

Claims 16 and 23-25 and 27-38 remain pending after entry of this amendment. Claims 16, 23-27, 29, 36 and 38 are presently amended. Claim 26 is cancelled.

Claim 16 is amended to set forth a method of killing a B cell lymphoma cell in a subject comprising administering a therapeutically effective amount of an immunoconjugate to the subject, wherein the immunoconjugate comprises an anti-CD20 antibody or an immunologic fragment thereof that binds to CD20 and is fused at its carboxy terminus to interferon-α-2a, and wherein the immunoconjugate binds to CD20 expressed by a B cell lymphoma cell in the subject and binds to an IFN-α-2a receptor expressed on the surface of an effector cell. Support for this amendment lies at least at the preceding versions of claim 16 and paragraphs **[0032]** and **[0034]** of the specification.

Claim 23 is amended to specify that the effector cell of claim 16 is selected from the group consisting of natural killer (NK) cells, lymphocyte-activated killer (LAK) cells, macrophages, monocytes, and polymorphonuclear (PMN) cells.

Claims 24 and 25 are amended to correct the antecedent basis of specified terms. Further, claims 24, 25 and 27 are amended to specify immunologic, rather than immunogenic, fragments (*see e.g.*, paragraph **[0034]** of the specification).

Claim 29 is amended to set forth a method of treating B cell lymphoma in a subject comprising administering a therapeutically effective amount of a immunoconjugate to the subject,

wherein the immunoconjugate comprises an anti-CD20 antibody or an immunologic fragment thereof fused at its carboxy terminus to interferon-α-2a, and wherein the immunoconjugate binds to CD20 expressed by a B cell lymphoma cell in the subject and binds to an IFN-α-2a receptor expressed on the surface of an effector cell. Support for this amendment lies at least at the preceding versions of claim 16 and paragraphs **[0032]** and **[0034]** of the specification.

Claims 36 and 38 are amended to correct antecedent basis and specify an "immunoconjugate" rather than "fusion protein" in accordance with the like amendment to claim 29.

Reconsideration in view of these amendments and following remarks is respectfully requested.

Rejection of claims 16 and 23-36 under 35 U.S.C. §112, first paragraph, enablement

Claims 16 and 23-36 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Official action, pp. 2-4. Specifically, the examiner alleges that the term "immunogenic fragment" covers antibody fragments that would not bind the antigen (*i.e.*, CD20) as set forth in the claims.

Claims 16 and 29 are amended to specify that the immunoconjugate comprises an anti-CD20 antibody or an immunologic fragment thereof that binds to CD20. Claim 26 is cancelled. As such, a skilled artisan would have no reason to doubt that the claimed immunoconjugates comprising an immunologic fragment of an anti-CD20 antibody would bind to CD20 because the newly amended claims specify that they bind to CD20.

The examiner also alleges that the pending claims fail to comply with the enablement requirement of 35 U.S.C. §112, first paragraph because claims 16 and 29 specify that the immunoconjugates possess human effector function. Newly amended claims 16 and 29 omit the phrase "human effector function".

Accordingly, withdrawal of the rejections of claims 16 and 23-36 under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejection of claims 16 and 23-32, 33, and 36-38 under 35 U.S.C. §103(a)

Claims 16, 23-32, 33, and 36-38 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Davis et al (2000) in view of Ozzello et al.. (1993). Official action, pp. 4-7.

The burden is on the examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co*., 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc*., 550 U.S. __, 82 USPQ2d 1385 (2007), the U.S. Supreme Court affirmed that this analysis includes the following factual inquiries: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art. The Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (USPTO Guidelines) state that, having undertaken the factual inquiries of *Graham*, a rejection under 35 U.S.C. § 103 may be supported by one or more of the following rationales: (1) combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of a known technique to improve similar methods in the same way; (4) applying a known technique to a known method ready for improvement to yield predictable results; (5) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (6) variations that would have been predictable to one of ordinary skill in the art; and (7) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention. 72 Fed. Reg. 57526, at 57529 (October 10, 2007).

Each of the above-noted rationales requires predictability in the art and/or a reasonable expectation of success, and the examiner must consider objective evidence that rebuts such predictability and reasonable expectation of success. The objective evidence or secondary considerations may include unexpected results and/or failure of others (*e.g.*, evidence teaching away from the currently claimed invention), evidence of commercial success, and long-felt but unsolved needs, as found in the specification as-filed or other source. *Id*. When considering the obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at __, 82 USPQ2d at 1396.

The applicants submit that the examiner fails to make a *prima facie* case because none of the cited references, either individually or taken together, are sufficient to render claims 16, 23-32, 33, and 36-38 obvious given that none of the rationales identified by the U.S. Supreme Court in *KSR* apply, and/or the objective evidence provided herein rebuts any alleged predictably or reasonable expectation of success.

(1) Combining prior art elements according to known methods to yield predictable results

Claim 16 is directed to a method of killing a B cell lymphoma cell in a subject comprising administering a therapeutically effective amount of an immunoconjugate to the subject, wherein the immunoconjugate comprises an anti-CD20 antibody or an immunologic fragment thereof that binds to CD20 and is fused at its carboxy terminus to interferon-α-2a, and wherein the immunoconjugate binds to CD20 expressed by a B cell lymphoma cell in the subject and binds to an IFN-α-2a receptor expressed on the surface of an effector cell. Claim 29 is directed to a method of treating a B cell lymphoma in a subject comprising the same steps as claim 16.

In the official action, the examiner alleges that Davis et al. "suggest that making a recombinant antibody or attaching another protein to a recombinant antibody at its carboxy terminus is well within the skill of an ordinary artisan before the effective filing date of the instant application." However, contrary to the examiner's allegation, nowhere in Davis et al. is there any teaching or suggestion of making or using a recombinant antibody conjugated to anything, much less conjugating an anti-CD20 antibody or immunologic fragment at its carboxy terminus to IFN-alpha-2a. Rather, Davis et al. describes the co-administration of two separate compounds (i.e., rituximab and IFN-2-2α) to non-Hodgkin's lymphoma patients. In view of what was known in the art at the time, immunoconjugating these two compounds would result in dosages of one or both compounds that would vary from the safe and effective amounts taught by Davis et al.. As such, a skill artisan would have no reasonable expectation that immunoconjugation of the two compounds would provide any benefit, and could in fact be detrimental, to the health of the patient.

The examiner cites Ozzello et al. and alleges that based upon Ozzello et al. a skilled artisan could readily determine a therapeutically effective amount of an immunoconjugate for administration in accordance with the claimed methods. To the contrary, Ozzello et al.

reinforces applicants' position that a skilled artisan would have no reasonable expectation of success in immunoconjugating an anti-CD20 antibody to IFN-2-2α as part of a therapeutically effective regimen for the treatment of B cell lymphoma.

For example, Ozzello et al. describes the preparation and dosages of an IFN-alpha/anti-Mc5 immunoconjugate administered to treat human mammary carcinoma xenografts in rats. On page 267, Ozzello et al. specifies that the nIFNα/Mc5 conjugate has $2x10^5$ IU, or 0.2 MIU, of nIFNα conjugated to 5 μg of Mc5 mAb. This is equivalent to administration of 400 MIU nIFNα /mg mAb.

In contrast, Davis et al. specifies that a safe and therapeutically effective regimen of rituximab and IFN-2-2α consists of 750 mg (or 375 mg/m^2) rituximab and 5 MIU of IFN-2-2α. This is equivalent to administration of 0.0067 MIU of IFN-2-2α /mg mAb.

Therefore, in view of Ozzello et al., a skilled artisan would conclude that a rituximab/IFN-2-2α immunoconjugate would in effect result in the administration of either 60,000 times less antibody or 60,000 times more IFN-2-2α than the safe and effective protocol taught by Davis et al. In view of the therapeutic dosages required for rituximab and the concerns regarding the systemic toxicity of IFN-α known at the time of filing, neither of these modifications can be considered to support a method of killing a B cell lymphoma cell, or method of treating a B cell lymphoma, in a subject comprising administering a therapeutically effective amount of an immunoconjugate to the subject, wherein the immunoconjugate comprises an anti-CD20 antibody or an immunologic fragment thereof that binds to CD20 and is fused at its carboxy terminus to interferon-α-2a, and wherein the immunoconjugate binds to CD20 expressed by a B cell lymphoma cell in the subject and binds to an IFN-α-2a receptor expressed on the surface of an effector cell (*i.e.*, claims 16 and 29).

Furthermore, a skilled artisan would question whether the observations regarding the therapeutic benefit of an IFN-alpha/anti-Mc5 immunoconjugate on human mammary carcinoma xenografts could predict the therapeutic benefit or effectiveness of anti-CD20/IFN-α-2a immunoconjugate used to treat B cell lymphoma, given the dramatic differences in activity among IFN-α species. *see* Specification, paragraph **[0002]**. For these reasons the applicants believe that the first rationale of the *Examination Guidelines* does not support the examiner's obviousness-type rejections of claims 16, 23-32, 33, and 36-38 under 35 U.S.C. §103(a).

(2) Simple substitution of one known element for another to obtain predictable results

Based upon the teachings of Davis et al., Ozzello et al., and the knowledge in the art at the time, the "predictable results" of simple substitution of an anti-CD20/IFN-α-2a immunoconjugate for the IFN-alpha/anti-Mc5 immunoconjugate described in Ozzello et al. would result in the administration to a subject of levels of anti-CD20 antibody or IFN-α-2a that would either lack therapeutic effectiveness, be unsafe, or both (*see e.g.,* Davis et al.). Thus, methods of killing a B cell lymphoma cell, or a methods of treating a B cell lymphoma, as set forth in the present claims would run contrary to the teachings of the cited art. For these reasons the applicants believe that the second rationale of the *Examination Guidelines* does not support the examiner's obviousness-type rejections of claims 16, 23-32, 33, and 36-38 under 35 U.S.C. §103(a).

(3) Use of a known technique to improve similar methods in the same way

A skilled artisan could not immunoconjugate an anti-CD20 mAb (*e.g.*, rituximab) to IFN-α-2a in a manner like that of Ozzello et al. and expect to achieve an improvement in the therapeutic efficacy of the combination treatment administered separately, because doing so would result in administration of levels of anti-CD20 antibody or IFN-α-2a that would either lack therapeutic effectiveness, be unsafe, or both, based upon the knowledge of skill in the art at the time (*see e.g.*, Davis et al.). Thus, the results achieved by the present invention are unpredictable based upon the prior art cited. For these reasons the applicants believe that the third rationale of the *Examination Guidelines* does not support the examiner's obviousness-type rejections of claims 16, 23-32, 33, and 36-38 under 35 U.S.C. §103(a).

(4) Applying a known technique to a known method ready for improvement to yield predictable results

A skilled artisan could not immunoconjugate an anti-CD20 mAb (*e.g.*, rituximab) to IFN-α-2a in a manner like that of Ozzello et al. and expect to achieve an improvement in the therapeutic efficacy of the combination treatment administered separately, because doing so would result in the administration to a subject of levels of anti-CD20 antibody or IFN-α-2a that would either lack therapeutic effectiveness, be unsafe, or both, based upon the knowledge of skill in the art at the time (*see e.g.,* Davis et al.). Thus, the results achieved by the present invention

are unpredictable based upon the prior art cited. Furthermore, there is no indication that the method of Davis et al. is "ready for improvement". For these reasons, the applicants believe that the fourth rationale of the *Examination Guidelines* does not support the examiner's obviousness-type rejections of claims 16, 23-32, 33, and 36-38 under 35 U.S.C. §103(a).

(5) Choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success

For the reasons discussed in the preceding analysis, a skilled artisan simply would have no reasonable expectation of successfully modifying either Davis et al. or Ozzello et al. in order to arrive at the presently claimed methods, given that the teachings are simply incompatible in arriving at safe and effective regimens of both an anti-CD20 antibody and IFN-α-2a. Accordingly, the applicants believe that the fifth rationale of the *Examination Guidelines* does not support the examiner's obviousness-type rejections of claims 16, 23-32, 33, and 36-38 under 35 U.S.C. §103(a).

(6) Variations that would have been predictable to one of ordinary skill in the art

Even if the immunoconjugates described in the claimed methods were viewed as a variation of the immunoconjugates of Ozzello et al., the claimed "variations" certainly would not have been predictable given that the ratios described in Ozzello et al. and the ratios described in Davis et al. are simply incompatible with a safe and effective method of kill in a B cell lymphoma cell or method of treating B cell lymphoma. For these reasons, the applicants believe that the sixth rationale of the *Examination Guidelines* does not support the examiner's obviousness-type rejections of claims 16, 23-32, 33, and 36-38 under 35 U.S.C. §103(a).

(7) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention

There is simply no teaching, suggestion, or motivation in the prior art that would have led a skilled artisan to adapt the teachings of Ozzello et al. to the teachings of Davis et al., given that such an adaptation would result in administration to a patient of an amount of anti-CD20 antibody and IFN-α-2a that either lacked therapeutic effectiveness, was unsafe, or both.

Based upon the foregoing, the applicants believe that the seventh rationale of the Examination Guidelines does not apply to the claimed methods. Further, the applicants assert that, prior to the present invention, the subject matter of claims 16, 23-32, 33, and 36-38 was neither described or could be reasonably predicted by one skilled in the art. Thus, the examiner has not established a *prima facie* case of obviousness. Withdrawal of the rejection of claims 16, 23-32, 33, and 36-38 under 35 U.S.C. §103(a) as allegedly unpatentable over the combination of Davis et al. in view of Ozzello et al. is respectfully requested.

Rejection of claims 25 and 32 under 35 U.S.C. §103(a)

Claims 25 and 32 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Davis et al (2000) in view of Ozzello et al. (1993) in further view of Shan et al. (1999). Official action, pp. 7-8. Other than Shan et al., the references the examiner cites in support of these alleged rejections have been previously discussed.

The examiner alleges that Shan et al. teach that IF5 is suitable for use in a IF5/interferon immunoconjugate. Official action, page 7. However, Shan et al. is directed to the characterization of scFv-Ig constructs generated from the anti-CD20 mAb 1F5 and fails to address the particular immunoconjugate specified in the claims, much less addressing the disparate dosing issues discussed with respect to Ozzello et al. and Davis et al.

As such, prior to the present invention, the subject matter of claims 25 and 32 was neither described or could be reasonably predicted by one skilled in the art. Thus, the examiner has not established a *prima facie* case of obviousness. Withdrawal of the rejection of claims 25 and 32 under 35 U.S.C. §103(a) as allegedly unpatentable over the combination of Davis et al. in view of Ozzello et al. in further view of Shan et al. is respectfully requested.

Rejection of claims 25 and 32 under 35 U.S.C. §103(a)

Claims 25 and 34 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Davis et al. (2000) in view of Ozzello et al. (1993) in further view of Haisma et al. (1998). Official action, pp. 8. Other than Haisma et al., the references the examiner cites in support of these alleged rejections have been previously discussed.

The examiner alleges that Haisma et al. teach that an IH4 single chain antibody is suitable for use in a IH4 single chain antibody/interferon immunoconjugate. Official action, page 8.

However, while Haisma demonstrates that IH4 can be immunoconjugated, Haisma fails to address the particular immunoconjugate specified in the claims, much less addressing the disparate dosing issues discussed with respect to Ozzello et al. and Davis et al.

As such, prior to the present invention, the subject matter of claims 25 and 34 was neither described or could be reasonably predicted by one skilled in the art. Thus, the examiner has not established a *prima facie* case of obviousness. Withdrawal of the rejection of claims 25 and 34 under 35 U.S.C. §103(a) as allegedly unpatentable over the combination of Davis et al. in view of Ozzello et al. in further view of Haisma et al. is respectfully requested.

Rejection of claims 25 and 32 under 35 U.S.C. §103(a)

Claims 25 and 35 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Davis et al (2000) in view of Ozzello et al. (1993) in further view of Vose et al. (2000). Official action, pp. 8-9. Other than Vose et al., the references the examiner cites in support of these alleged rejections have been previously discussed.

The examiner alleges that Vose et al. teach that tositumomab is suitable for use in a tositumomab/interferon immunoconjugate. Official action, page 8. However, Vose et al. fails to address the particular immunoconjugate specified in the claims, much less addressing the disparate dosing issues discussed with respect to Ozzello et al. and Davis et al.

As such, prior to the present invention, the subject matter of claims 25 and 35 was neither described or could be reasonably predicted by one skilled in the art. Thus, the examiner has not established a *prima facie* case of obviousness. Withdrawal of the rejection of claims 25 and 35 under 35 U.S.C. §103(a) as allegedly unpatentable over the combination of Davis et al. in view of Ozzello et al. in further view of Vose et al. is respectfully requested.

Conclusion

All rejections having been addressed, it is respectfully submitted that claims 16, 23-25, and 27-38 are in condition for allowance and a Notice to that effect is earnestly solicited. If helpful to expedite prosecution, the examiner is kindly requested to contact the undersigned at the telephone number listed below.

The required fees for the petition for extension of time are submitted herewith via EFS Web charge authorization. Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,
PILLSBURY WINTHROP SHAW PITTMAN LLP

/ Russell S. Timm /
By:_____
Russell S. Timm, Ph.D.
Registration No. 55,677

October 3, 2008
P.O. Box 10500
McLean, VA 22102
(703) 770-7713 Direct Dial
(703) 770-7901 Facsimile